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Interdental Papilla Loss: Comparison between Hyaluronic Acid VS Platelet-Rich Fibrin

Integrative Systematic Review

Maria Nunes de Figueiredo Vieira Borges

Dissertação conducente ao **Grau de Mestre** em **Medicina Dentária (Ciclo Integrado)**

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Trabalho realizado sob a Orientação de **Professora Doutora Paula López Jarana**

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Eu, acima identificado, declaro ter atuado com absoluta integridade na elaboração deste trabalho, confirmo que em todo o trabalho conducente à sua elaboração não recorri a qualquer forma de falsificação de resultados ou à prática de plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria do trabalho intelectual pertencente a outrem, na sua totalidade ou em partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores foram referenciadas ou redigidas com novas palavras, tendo neste caso colocado a citação da fonte bibliográfica.

ABSTRACT

Introduction: nowadays, the absence of the interdental papilla leads to an aesthetic discomfort and affects self-esteem in some patients. It can lead to caries lesions and phonetic alterations. Thus, dentists have developed surgical and non-surgical techniques to treat this loss of papilla.

Objective: is to know which is the best non-surgical technique, between Hyaluronic Acid and Platelet-Rich Fibrin, that restores the deficient interdental papilla.

Materials and Methods: we used several databases, such as Pubmed, Cochrane, ScienseDirect and Lilacs. A review of the selected articles dated from 2013 to the present was carried.

Results: the search resulted in a total of 1246 and after analysis, 27 articles were selected for this systematic review.

Discussion: the ideal conditions for treating a black triangle are a thick gingival phenotype, a higher interproximal papilla height or a smaller black triangle and HA presents better results as restoring material. It is essential to have good oral hygiene to accompany this treatment and to be as successful as possible.

Conclusion: the existence of a biological barrier, such as the interdental papilla, is important. Its restoration, therefore, is essential. We concluded that HA at this time is the most effective choice. PRF still needs to be further studied to be a viable choice. It is important to remember that as they are biodegradable substances, continued filling is required.

Key-Words: *interdental papilla loss, aesthetics, treatment, hyaluronic acid, platelet-rich fibrin, dental papilla reconstruction.*

RESUMO

Introdução: atualmente, a ausência da papila interdentária afeta a autoestima e leva ao desconforto estético em alguns pacientes. Pode levar a lesões de cárie e alteração da fonética. Desta forma, os médicos-dentistas têm desenvolvido técnicas cirúrgicas e não-cirúrgicas para tratar esta perda de papila.

Objetivo: é saber qual é a melhor técnica não cirúrgica, entre o Ácido Hialurónico e a Fibrina Rica em Plaquetas, que restauram a papila interdentária deficiente.

Materiais e Métodos: utilizamos várias bases científicas, como o Pubmed, Cochrane, ScienseDirect e Lilacs. Foi feita a revisão dos artigos selecionados, datados desde 2013 até ao ano presente.

Resultados: a pesquisa resultou num total de 1246 e após análise, 27 artigos foram selecionados para a realização desta revisão.

Discussão: as condições ideais para tratar um triângulo negro são um fenótipo gengival espesso e uma altura papilar interproximal maior ou um triângulo negro mais pequeno. O HA apresenta melhores resultados como material restaurador. É essencial ter uma boa higiene oral para que este tratamento tenha o maior sucesso possível.

Conclusão: a existência de uma barreira biológica, como é a papila interdentária, é importante. A sua restauração, portanto, é essencial. Concluímos que o HA neste momento é a escolha mais efetiva. O PRF ainda necessita ser mais estudado para ser uma escolha viável. É importante relembrar que como são substâncias biodegradáveis, é necessário um preenchimento continuado.

Palavras-Chave: *perda da papila interdental, estética, tratamento, ácido hialurónico, fibrina rica em plaquetas, reconstrução da papila interdentária.*

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LIST OF ACRONYMS AND ABBREVIATIONS

BT: Black Triangles

C: Control

CP-PT Distance: Contact-Point – Papilla Tip Distance

CTG: Connective Tissue Graft

GT: Gingival Thickness

HA: Hyaluronic Acid

KTW: Keratinized Tissue Width

PPI: Papilla Presence Index

PRF: Platelet-Rich Fibrin

STF: Split-Thickness Flap

1 - INTRODUCTION

More than ever before, an esthetic smile is required by patients since affects their interpersonal relationships and patient self-esteem (1,2).

There are sophisticated techniques to create "white esthetics" but the successful reconstruction of "pink esthetics" remains a challenge for doctors, especially in the interdental area (3). Even so small, has a significant importance from an esthetic perspective during smile, mainly in the anterior teeth, and should stand out with firm consistency, pink colour and triangle shape (1,4).

The interdental papilla has particular anatomical and histological characteristics (5) which makes it more susceptible to overgrowth when compared to attached and marginal gingivae (6). Unfortunately, with minor blood supply makes it limit to reconstruct with the different non-surgical and surgical techniques (5).

Papilla is composed by a dense connective tissue containing fibers, vessels and nerves, and covered by oral keratinized epithelium – externally – and junctional and oral sulcular epithelium – internally – attached to the tooth and bone by supragengival fibers and its vascularization derives from the interdental septa, the periodontal ligament, and the oral mucosa (7).

Changes that include alterations of dimension or loss of the papilla (gingival black triangles) were considered as the third less attractive problem after visible caries and exposed crown margins (6). Its morphology is multifactorial, determined by age, hygiene, teeth's size and shape, distance between roots, root angulation, crestal bone height, presence/absence of periodontal disease, alveolar crest-interdental contact point distance and periodontal phenotype (7–9).

Acts as biological barrier since it protects from root caries, food and plaque accumulation, bad breath, gingivitis and altered word pronunciation – allowing the passage of air and saliva, so it is crucial its presence (4,5,10,11).

Due to its limited potential in regenerating itself compared to other parts of the gingiva, research in non-surgical and surgical treatments were developed. Surgical methods are not only unpredictable, the degree of success and stability is varied, is invasive with increased patient morbidity – all this without a guarantee of a successful regeneration, since it is so narrow, with complicated access and reduced blood supply in that area (1,5,7,12). Consequently, non-surgical approaches were proposed including Hyaluronic Acid and Platelet-rich fibrin.

Hyaluronic Acid is an essential glycosaminoglycan of high density found in several body fluids such as saliva, synovial fluid, extracellular matrix of soft connective tissues, and the lowest in blood serum. Discovered in 1934, is biocompatible – does not have antigenic specify for tissues – bacteriostatic and fungistatic – has viscoelastic properties delaying the penetration of bacteria and viruses – anti-inflammatory, anti-oedematous, osteoinductive, proangiogenic, antioxidant, stimulates angiogenesis, proliferative and soothing properties. Maintains the structural and homeostatic integrity of tissues by regulating osmotic pressure and enhancing tissue lubrification and resiliency; amplifies the migration of gingival fibroblasts, the principal cell in gingival connective tissue; presents hygroscopic since 1g HA can bind up to 61 of water; also, is antiseptic and favourable to decrease bleeding. However, there are a few contradictions that will be referred throughout this review (5,13–20).

Platelet-rich fibrin is a second-generation platelet concentrate. Assists in tissue regeneration – considering the existence of regenerative cells, white blood cells, leading to higher concentrations of growth factors; periodontal defects and gingival recession treatment. Instigate, as well, higher fibroblasts migration and angiogenesis promoting wound healing. PRF is developed per centrifugation of blood acquired in glass tubes without anticoagulants and activators, considered easy to prepare (16,21,22).

HA and PRF have plenty of similarities when it comes to promote regeneration, collagen synthesis and wound healing. Throughout this systematic review, we will proceed to compare and comprehend their effects, results and efficacy to determinate if both or which one can be embraced as a primary nonsurgical treatment of interdental papilla loss (16).

2 – OBJECTIVE

2.1) Principal objective:

The primary objective is to know which technique Hyaluronic Acid or Platelet-rich Fibrin restores best the loss of interdental papilla or “black triangles”.

2.2) Secondary objective:

The secondary objective is how is guaranteed and which parameters are necessary to validate its efficacy and maintenance in the course of time.

2.3) Hypothesis:

Hyaluronic Acid presents better treatment results compared to Platelet-Rich Fibrin.

2.4) Null Hypothesis:

There is no difference between treating the black triangles with Hyaluronic Acid or Platelet-Rich Fibrin.

3 – MATERIALS AND METHODS

3.1) PROTOCOL DEVELOPED AND ELIGIBILITY CRITERIA

A protocol was developed according to the PRISMA statement for our Integrative Review type study.

3.2) PICO QUESTION:

The main question was developed according to the study design, population, intervention, comparison and outcome (PICO). The following question was formulated to guide the research:

"Which of the non-invasive techniques, hyaluronic acid or platelet-rich fibrin, presents better short- and long-term results?"

3.3) FOCUS OF THE PICO QUESTION

The criteria applied to the PICO question are:

P (population)	Patients with interdental papilla loss
I (interest)	Use a non-surgical technique to restore the interdental papilla
C (context)	Compare techniques: Hyaluronic Acid VS Platelet-rich Fibrin
O (outcome)	What are the variables and how do they allow the results to be assessed?

Table 1 - PICO search strategy.

3.4) DATA BASE AND KEYWORDS

Bibliographic research carried out through the database PubMed, ScienceDirect, Lilacs, Cochrane, using MeSH terms and normal research, as the keywords: [interdental papilla], [interdental papilla loss], [hyaluronic acid], [aesthetics, dental], [angiogenesis], [injection], [treatment], [black triangles], [gingiva], [platelet-rich fibrin], [dental papilla] and [dental papilla reconstruction].

The search strategy with the keyword combinations is below (Table 2).

Database	Search Strategy	Search Data	Identified Articles
ScienceDirect	(hyaluronic acid) AND (black triangles) AND (interdental papilla)	15-01-2023 to 06-03-2023	15

Pubmed	(hyaluronic acid[MeSH Terms]) AND (interdental papilla[MeSH Terms])	15-01-2023 to 06-03-2023	81
Pubmed	(hyaluronic acid) AND (black triangles) AND (interdental papilla)	18-01-2013 to 18-01-2023	24
Cochrane	(hyaluronic acid) AND (black triangles)	28-01-2023 to 28-01-2023	8
Lilacs	(hyaluronic acid) AND (interdental papilla)	20-02-2023 to 06-03-2023	8
Pubmed	(hyaluronic acid) AND (angiogenesis)	20-02-2023 to 20-02-2023	676
Pubmed	(black triangles) AND (treatment) AND (injection)	22-02-2023 to 22-02-2023	44
Cochrane	(interdental papilla loss) AND (treatment)	22-02-2023 to 22-02-2023	54
Pubmed	(dental papilla reconstruction)	12-03-2023 to 12-03-2023	280
Pubmed	(platelet-rich fibrin) AND (dental papilla)	15-03-2023 to 15-03-2023	13
Pubmed	(interdental papilla[MeSH Terms]) AND (platelet-rich fibrin[MeSH Terms])	17-03-2023 to 17-03-2023	43

Table 2 - Search strategy for the bibliographical research carried out.

3.5) INCLUSION AND EXCLUSION CRITERIA

The following table (Table 3) sets out the inclusion and exclusion criteria that dictated the filtering of the articles obtained:

Inclusion Criteria	Exclusion Criteria
Articles between 2013-2023;	Articles before 2013;
In English, Portuguese or Spanish;	Other languages;
Research in humans.	Research in other species.

Table 3 - Inclusion and exclusion criteria of the literature search carried out.

3.6) ARTICLE SELECTION

According to the strategy mentioned above, the database search resulted in a total of 1246 articles identified. The articles initially went through a process of identifying duplicates, resulting in 1195 articles available for screening. Next, using automated tools, 667 articles were excluded, resulting in 528 publications to be analysed. After reading the titles and abstracts, 34 articles were selected, and of these 34, 7 articles were excluded after full reading for addressing implants, recessions, and no relevant information. Finally, 27 articles were included in this dissertation.

In order to obtain more complete research, a flowchart (Figure 1) based on the PRISMA 2020 Template was also carried out.

4 – RESULTS

Following the search criteria, this systematic review included 27 studies, of which 9 are reviews, 6 clinical studies, 3 clinical trials, 5 case reports, 1 pilot study and 3 comparative studies. The inclusion and exclusion criteria are presented in the Materials and Methods section.

From each eligible study included in the present systematic review, was collected data about its general characteristics, such as the year of publication and setting, involved participants, classification of interdental papilla loss and its causes, periodontal phenotype, what material was injected (characteristics) and how (quantity and frequency).

Of the 18 articles selected for analyses of results, the following points are covered:

- ⇒ 1 (5.5%) is about the characteristics of the interdental papilla and causes of black triangles;
- ⇒ 8 (44.4%) are about restoring the interdental papilla injecting Hyaluronic Acid, also HA with an overlay technique;
- ⇒ 2 (11.1%) are comparative, one of them is about comparing two different Hyaluronic Acids and the other is about comparing Hyaluronic Acid VS physiological saline;
- ⇒ 1 (5.5%) is about reporting an adverse reaction after hyaluronan injection;
- ⇒ 4 (22.2%) are about using Platelet-rich Fibrin to regenerate the interdental papilla, using PRF with connective tissue and PRF with microneedling;
- ⇒ 1 (5.5%) is about comparing Platelet-rich Fibrin with connective tissue graft;
- ⇒ 1 (5.5%) is about comparing Hyaluronic Acid and Platelet-rich Fibrin;

The main data and results are present in Table 4.

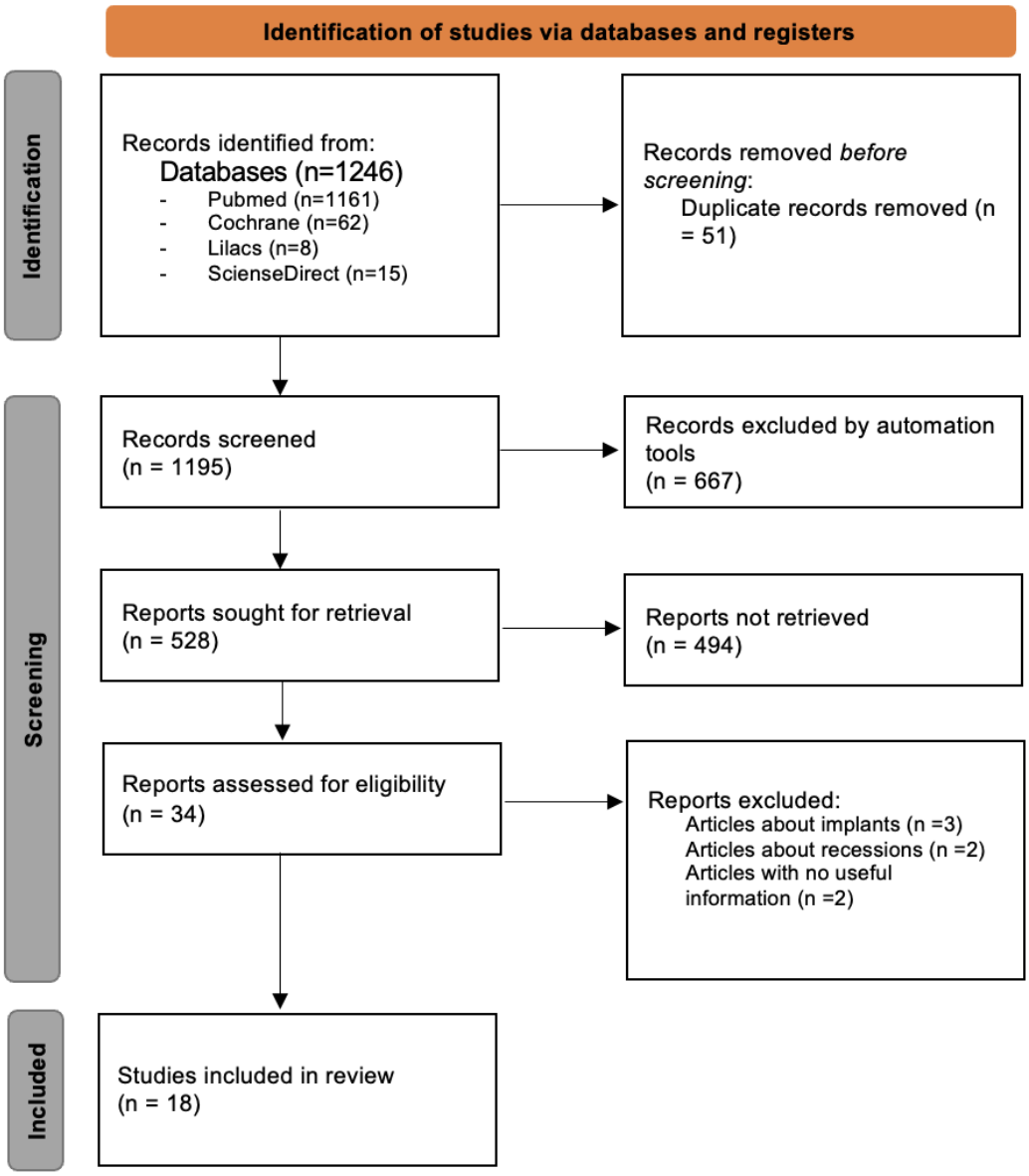

Figure 1 - Flowchart of the literature search based on the PRISMA 2020 Template.

ARTICLE	OBJECTIVE	SUBSTANCE INJECTION	QUANTITY OF ADIMINSTRA-TION PER PAPILLA	QUANTITY OF SESSIONS	FOLLOW-UP	INITIAL AND FINAL MEASURES	RESULTS	SYMPTOMS	CONCLUSION
Title: Adverse reaction after hyaluronan injection for minimally invasive papilla augmentation. A report on two cases Authors: Bertl K, Gotfredsen K, Jensen S, Bruckmann C, Stavropoulos A Year: 2016 Type of Study: Case report	Adverse reactions after hyaluronan injection around natural and implant teeth – report two cases, focusing on the regeneration of the interdental papilla.	Hyaluronan (1mL gel contains 16mg cross-linked Na-hyaluronate and 2mg Na-hyaluronate)	0,18mL + 0,12mL+ 0,06mL –> 0,36mL	2	2 months	-	Both patients presented swelling and extreme sensivity with a burning sensation on the lip near the injection area after the second session. Discoloration of the skin – livedo reticularis – was also observed in one of the patients. The symptoms lasted up to 7 days without any permanent damage.	Swelling, tenderness, discoloration (livedo reticularis): lasted for 7 days	The highly hygroscopic HY leads to water attraction throughout time, and generates an external vascular compression and partial occlusion of some blood vessels near. Was very improbable to be an infection or an allergic reaction.
Title: Use of hyaluronic acid as an alternative for reconstruction of interdental papilla Authors: Corte Sánchez D, Yáñez Ocampo B, Esquivel Chirino C Year: 2017 Type of Study: Case Report	Clinical case about interdental papilla reconstruction with HA infiltration.	Hyaluronic Acid	1mL	4 (0, 7, 14, 21 days)	-	-	At first, HA did not fully cover interproximal space. When treatment was complete, the papilla covered all the space. Before HA injection: IPP2 After HA injection: IPP1	-	HA is one of the non-surgical methods to regenerate interdental papilla. Several researches were conducted throughout time, but others factors have to be considered; as well bigger populations, with different ethnicities, gender and using different infiltration intervals.

Title: The use of hyaluronic acid as an adjuvant in the management of periodontitis Authors: Lopez M, Casale M, Condotto V Year: 2017 Type of Study: Pilot Study	Present a case using HA to reconstruct interdental papilla.	Hyaluronic Acid	1 mL	4	15 days	-	The interdental papilla classification was initially IPP2, and after treatment was considered IPP1. The results with the use of HA were favourable.	-	Interdental soft tissue assessment and the distance between the bone crest and the contact point is necessary. When the distance bone crest – contact point is 5mm or less, and the height of the papilla does not exceed 4mm, an intervention is justified. There is the possibility to use HA, predictably, to regenerate the interdental papilla.
Title: Augmentation of interdental papilla with platelet-rich fibrin Authors: Ahila E, Saravana R, Reddy V, Pratebha B, Jananni M, Priyadharshini V Year: 2018 Type of Study: Clinical Study	Evaluation of the interdental papilla augmentation with platelet-rich fibrin.	PRF	-	1	6 months	yes	Distance from the contact point to the tip of the gingival margin Baseline: 4.28mm 3 months: 2mm 6 months: 0.30mm Width of keratinized gingiva Baseline: 6.29mm 3 months: 7.84mm 6 months: 8.68mm Jemt Score Baseline: 1 3 months: 2.96 6 months: 3 Healing Index 1 week: 3 2 weeks: 3 3 weeks: 4	-	Using PRF was successful in the management of papillary loss, when reviewed at 3 and 6 months after. Their technique, with loupes, reduced tissue trauma and better operator's comfort.

Title: Papilla reconstruction: interdisciplinary consideration for clinical success Authors: Carnio J, Carnio A Year: 2018 Type of Study: Case Report	Describes how an interdisciplinary approach works into treat a patient with papilla loss.	-	-	-	6 months	-	Considered a success due to the initial problem after 2 years. The recession on both teeth was completely covered and the interproximal space was filled with natural looking soft tissue. The clinical attachment level increased 4mm on the medial aspect of tooth #7 and 3mm on the distal aspect of tooth #8. It is expected that the nature of this attachment to the root surface is mediated by a junctional epithelium combined with connective tissue fiber adhesion.	-	Understand the principles among specialists to diagnose and treat the finest way.
Title: Remodelación de papilla gingival interdental con ácido hialurónico. Una solución estética Authors: Iribarra-Leigh J, Soto-Royo M, Rubio-Muñoz M, Torres-Castillo O, Baldeig L,	Evaluate the effect of hyaluronic acid in gingival papilla in the anterior sector with black triangle defects, in a periodontal treated patient.	Hyaluronic Acid Gel	0,15mL total (0,05mL each session)	3	2 months	yes	Percentage of papillary filling 1.3-1.2: 56% 1.2-1.1: 56% 1.1-2.1: 100% 2.1-2.2: 56% 2.2-2.3: 56% Vertical Measurements of the Papillae (amount of mm achieved) 1.3-1.2: 1mm 1.2-1.1: 2mm	-	Hyaluronic acid application is effective when there is a Class I Nordland and Tarnow, bur not that effective about the Class II and III. An application every 6 months allows to maintain aesthetics results over time.

Gómez-Morales A Year: 2019 Type of Study: Clinical Report							1.1-2.1: 2mm 2.1-2.2: 2mm 2.2-2.3: 1mm		
Title: Assessment of Hyaluronic Acid Gel Injection in the Reconstruction of Interdental Papilla: a Randomized Clinical Trial Authors: Abdelraouf S, Dahab O, Elbarbary A, El-Din A, Mostafa B Year: 2019 Type of Study: Clinical Trial	Evaluate the efficacy of hyaluronic acid gel to reconstruct deficient interdental papilla.	Hyaluronic Acid Gel (concentration of 20 mg/mL) VS Saline	0,1mL	3 (baseline, 3 and 6 weeks)	6 months	yes	**HA GROUP** Height of black triangles Baseline – 3M: -0.31mm 3M – 6M: -0.06mm Baseline – 6M: -0.23mm Surface area of the Black Triangle Baseline – 3M: -36.5% 3M – 6M: -11.8% Baseline – 6M: -45% Satisfaction score (at 6 months): 45 **SALINE GROUP** Height of black triangles Baseline – 3M: -0.07mm 3M – 6M: 0.04mm Baseline – 6M: -0.03mm Surface area of the Black Triangle Baseline – 3M: -0.9% 3M – 6M: 0.9% Baseline – 6M: -2.0% Satisfaction score (at 6 months): 27.86	-	Using hyaluronic acid gel to reconstruct interdental papilla loss is effective along with patients' satisfaction.

Title: Subperiostal Papilla Augmentation with a Non-Animal-Derived Hyalurionic Acid Overlay Technique Authors: Spano S, Ghilzon R, Lam D, Goldberg M, Tenenbaum H Year: 2019 Type of Study: Clinical Study	To illustrate a minimally invasive approach to restore interdental papilla deficiencies.	Hyaluronic Acid	0,2 to 0,6mL	1	6 months	yes	Papilla Defect Pretreatment C1: 3mm C3: 5.5mm C2: 4mm C4: 2mm Papilla Defect 6 Weeks Posttreatment C1: 1mm C3: 4mm C2: 1.5mm C4: 1mm Papilla Defect 6 Months Posttreatment C1: 1mm C3: 3.5mm C2: 2mm C4: 1mm	-	With this overlay technique, was demonstrated the restoration of deficient interdental papilla.
Title: Efficacy Evaluation of Hyaluronic Acid Gel for the Restoration of Gingival Interdental Papilla Defects Authors: Ni J, Shu R, Li C Year: 2019 Type of Study: Clinical Study	Evaluate the long-term efficacy with hyaluronic acid gel for gingival interdental papilla.	Hyaluronic acid gel (16 mg/mL)	0,05 to 0,1 mL	3 (0, 3, 6 weeks)	12 months	yes	**THICK GINGIVAL PHENOTYPE** Increased Height of the Gingival Papilla 3M: 0.311mm 6M: 0.45mm 12M: 0.4mm Decreasing the Surface of the Black Triangle 3M: 0.31mm2 6M: 0.41mm2 12M: 0.36mm2 **THIN GINGIVAL PHENOTYPE** No statistically difference	-	Hyaluronic acid gel is effective in restoring the deficient gingival papilla. More effective in thick gingival phenotype. Not useful in thin gingival phenotype. Better results at 6 months than at 12 months.
Title: An examination of the 2-year results obtained from	Compare and evaluate the clinical results using digital	Hyaluronic Acid Gel	0,1mL	3 (0, 3, 6 weeks)	24 months	yes	**Interdental Space Area (mm^2)** Maxilla B: 0.30	-	The study was a success with the application of hyaluronic acid

hyaluronic acid filler injection for interdental papilla losses Authors: Turgut Çankaya Z, Tamam E Year: 2020 Type of Study: Clinical Study	impressions after applicating hyaluronic acid fillers for the reconstruction of papillary losses.	(2mg/mL HA non-cross-linked and 16mg/mL HA cross-linked)					3M: 0.14 1Y: 0.08 2Y: 0.06 Mandibula B: 0.24 3M: 0.10 1Y: 0.08 2Y: 0.05		filler to reconstruct multiple papillae. Also, the results showed throughout time the maxilla has a quickly and higher-level outcome.
Title: Interdental papilla reconstruction using injectable hyaluronic acid: a 6 month prospective longitudinal clinical study Authors: Alhabashneh R, Alomari S, Khaleel B, Qinawi H, Alzaubi M Year: 2020 Type of Study: Clinical Study	Evaluate the efficacy of Hyaluronic Acid on interdental papilla loss in the aesthetic sector.	Hyaluronic Acid Gel	-	2 (after 3 weeks)	6 months	yes	**BLACK TRIANGLE HEIGHT** Maxilla 3 weeks: 1.793mm 3 months: 0.974mm 6 months: 1.199mm Mandible 3 weeks: 1.893mm 3 months: 1.536mm 6 months: 1.714 mm Class I 3 weeks: 1.707 mm 3 months: 0.966 mm 6 months: 1.105 mm Class II 3 weeks: 1.886 mm 3 months: 1.254 mm 6 months: 1.500 mm	-	Using hyaluronic acid is a promising technique over the first 6 months after injection. The maximum result was at 3 months with a reduction between 3 and 6 months.
Title: Injectable platelet-rich fibrin and microneedling for gingival	Evaluate the effect of gingival thickness and keratinized	Platelet-Rich Fibrin VS	-	4 (0, 10, 20, 30 days)	6 months	yes	**GT** C/PRF/MN+PRF B: 0.41 / 0.43 / 0.40	-	In patients with thin periodontal phenotype, both these techniques are beneficial in

augmentation in thin periodontal phenotype: a randomized controlled clinical trial Authors: Ozsagir Z, Saglam E, Sen Yilmaz B, Choukroun J, Tunali M Year: 2020 Type of Study: Clinical Trial	tissue width using injectable platelet-rich fibrin and with microneedling in patients with thin periodontal phenotypes.	Platelet-Rich Fibrin with Microneedling					1M: 0.62 / 0.61 / 0.62 2M: 0.61 / 0.60 / 0.63 3M: 0.64 / 0.62 / 0.65 4M: 0.63 / 0.62 / 0.64 5M: 0.65 / 0.63 / 0.66 6M: 0.64 / 0.62 / 0.66 **KTW** C/PRF/MN+PRF B: 2.96 / 2.98 / 2.94 1M: 2.97 / 2.99 / 2.95 2M: 2.97 / 2.99 / 2.96 3M: 2.98 / 2.99 / 2.97 4M: 2.99 / 2.99 / 2.98 5M: 2.99 / 2.99 / 2.98 6M: 2.99 / 2.99 / 2.99		increasing Gingival Thickness. Results indicate PRF + MN may be a first non-surgical technique to use.
Title: Efficacy of Platelet-rich Fibrin in Interdental Papilla Reconstruction as Compared to Connective Tissue Using Microsurgical Approach	Evaluate autologous platelet-rich fibrin and autogenous connective tissue graft in interdental papilla reconstruction using	Autologous platelet-rich fibrin AND Autogenous connective tissue graft	-	1	3 months	yes	**Gingival Index** Group 1(STF+PRF) B: 1.34 1M: 1.20 3M: 1.02 Group2(STF+CTG) B: 1.31 1M: 1.25 3M: 1.09 **Papilla Index Score**	-	Using STF along PRF or CTG is a successful procedure to increase interdental papilla height.

Authors: Singh D, Jhingran R, Bains V, Madan R, Srivastava R Year: 2020 Type of Study: Comparative Study	microsurgical technique.						Group 1(SRF+PRF) B: 1.50 1M: 2.80 3M: 2.80 Group2(STF+CTG) B: 1.45 1M: 2.20 3M: 2.95		
Title: Comparative Evaluation of Two Hyaluronic Acid Gel Products for the Treatment of Interdental Papillary Defects Authors: Mandel I, Farkasdi S, Varga G, Nagy Á Year: 2020 Type of Study: Comparative Study	Investigate the effectiveness of single injections of two different hyaluronic acids (Flex Barrier and Revident) to reduce black triangles in Class I and II Nordland-Tarnow recessions.	2 Hyaluronic Acids	0,1mL	1	1 month	yes	**Revident** Maxilla Immediately after: 79.4 1 week: 88.0 1 month: 90.3 Mandible Immediately after: 82.7 1 week: 81.35 1 month: 81.5 **Flex Barrier** Maxilla Immediately after: 81.8 1 week: 91.6 1 month: 97.5 Mandible Immediately after: 86.0 1 week: 90.7 1 month: 94.4	-	Both are effective in reducing black triangles' size, although Revident had longer-lasting improvements. Class I has better results than Class II.
Title: Hyaluronic acid vs. physiological saline for enlarging deficient gingival papillae: a randomized controlled clinical	Evaluate the efficacy of the injection of hyaluronic acid and compare to physiological saline solution in deficient gingival	Hyaluronic Acid AND Physiological Saline	0,05-0,1mL	3 (0, 3, 6 weeks)	12 months	yes	**The height of gingival papilla** Control group B: 2.99 mm 6M: 3.12 mm 12M: 3.26 mm Test group B: 3.25 mm 6M: 3.45 mm	-	Using hyaluronic acid is an effective treatment to increase the height of gingival papillae to enhance gingival papilla defects. Although, the

trial and an in vitro study Authors: Ni J, Zhong Z, Wu Y, Shu R, Wu Y, Li C Year: 2021 Type of Study: Comparative Study	papillae restoration in vivo and in vitro.						12M: 3.53 mm **The area of black triangle** Control group B: 1.78 mm 6M: 1.63 mm 12M: 1.46 mm Test group B: 1.90 mm 6M: 1.65 mm 12M: 1.45 mm		effect is not superior to that of physiological saline solution.
Title: Evaluation of the Hyaluronic Acid Versus the Injectable Platelet-Rich Fibrin in the Management of the Thin Gingival Phenotype: A Split-Mouth Randomized Controlled Clinical Trial Authors: Faour N, Dayoub S, Hajeer M Year: 2022 Type of Study: Clinical Trial	Evaluate the effect of multiple injections of hyaluronic acid on thin gingival phenotype and compare this effect with that resulting from multiple injections of the PRF.	Hyaluronic Acid (2mg HA and 16mg cross-linked HA) AND Platelet-Rich Fibrin	-	3 (0, 1, 2 weeks)	3 months	yes	**Gingival Thickness** i-PRF Group B-1M: 0.762-1.02 B-3M: 0.762-1.05 1M-3M: 1.02-1.05 HA Group B-1M: 0.753-1.057 B-3M:0.753-1.09 1M-3M: 1.057-1.09 **Keratinized Tissue Width** i-PRF Group B-1M: 4.06-4.07 B-3M: 4.06-4.07 1M-3M: 4.07-4.07 HA Group B-1M: 4.05-4.08 B-3M: 4-05-4.09 1M-3M: 4.08-4.09 **Gingival Index** i-PRF Group B-1M: 0.664-0.542 B-3M:0.664-0.571 1M-3M0.542-0.571 HA Group B-1M: 0.664-0.542 B-3M: 0.664-0.571 1M-3M:0.542-0.571	-	Multiple injections of PRF and HA in the thin gingival phenotype in an increased Gingival Thickness and increased Keratinized Tissue Width. Both techniques were more successful in improving the GT than the KTW.

Title: A novel injectable platelet-rich fibrin reinforced papilla reconstruction technique Authors: Puri K, Khatri M, Bansal M, Kumar A, Rehan M, Gupta A Year: 2022 Type of Study: Case Report	Evaluate clinically the use of injectable platelet-rich fibrin as a non-surgical technique for the interdental papilla reconstruction.	Platelet-Rich Fibrin	-	1	6 months	-	- decrease in CP-PT distance and area of the black triangle measurements after 1, 3, 6 months. Clinical examinations: - 3 sites: 100% - 1 site: 75% - 2 sites: 66.6%	-	PRF due to its autologous healing biomaterial is effective to improve and treat deficient interdental papilla.
Title: Efficacy of platelet-rich fibrin and connective tissue graft in papilla reconstruction Authors: Ozcan Blulut S, Ilhan D, Karabulut E, Caglayan F, Keceli H Year: 2022 Type of Study: Clinical Study	Evaluate and compare efficacy of PRF and CTG in reconstructing the papilla using a semilunar technique	Platelet-Rich Fibrin AND Connective Tissue Graft	-	1	6 months	yes	CTG provided better PR outcomes. GI, PI and PD showed a slight increase at T_1 and then, turned to their BL levels. The other periodontal parameters showed significant improvement after both treatment modalities. No inter-group difference was found except for KTW, which as in favour of CTG.	-	CTG is recommended over PRF because of its results.

Table 4 - Results Table.

5- DISCUSSION

The loss of papillae and consequent creation of the black triangle can be generated by pathological situations that lead to aesthetic disharmony in the patient's smile.

The histomorphometric characteristics of the papillary tissue and its three-dimensional position represent a treatment challenge for any specialist. We try to investigate which are the ideal conditions of the interdental papilla to be restored, which is the best material – Hyaluronic Acid or Platelet Rich Fibrin – and to understand the short- and long-term results.

The classification of interdental papillae, the influence of the periodontal phenotype, the importance of evaluating the inclusion criteria and the results obtained with Hyaluronic Acid and Platelet Rich Fibrin will be discussed.

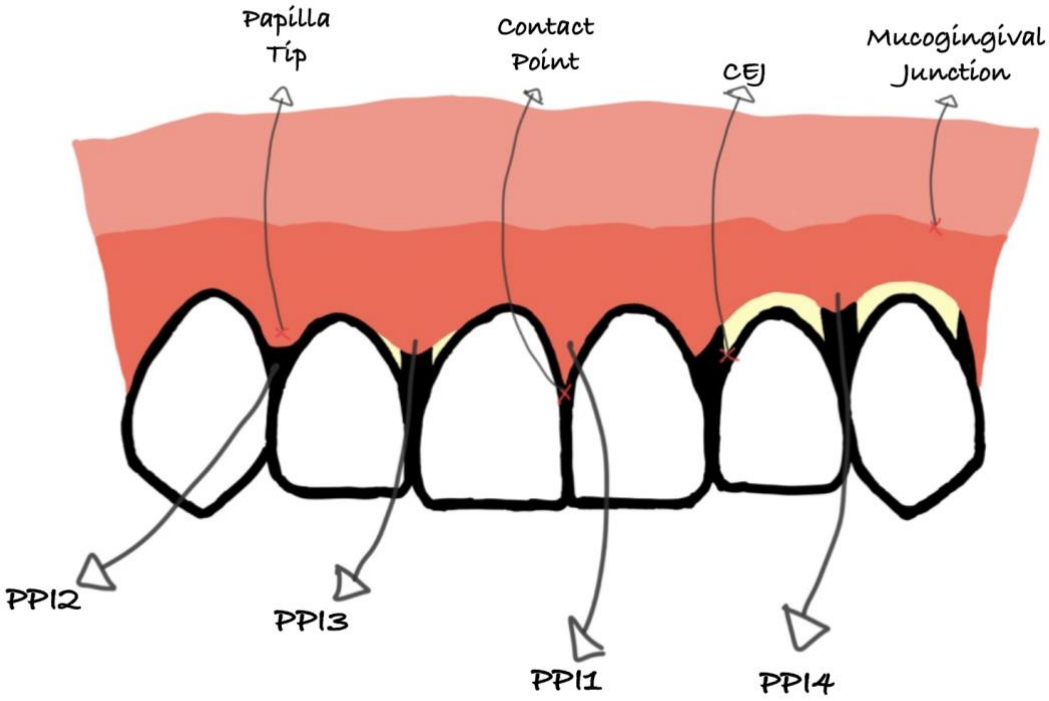

Figure 2 - Illustration of the PPI.

5.1) Interdental Papilla Classification

Almost all articles who classified the interdental papilla used Nordland and Tarnow classification, although the new system currently used to assess the height of the interdental papilla in natural teeth is the Papilla Presence Index (PPI). When comparing two hyaluronic acid gel products, Mandel et al. concluded that with only one application, there was an increase in papilla height in patients with classes I and II by the Nordland and Tarnow classification, better in class I (3). Likewise, in Spano et al and Irribarra-Leight et al. studies were showed a more favourable response in patients with Nordland and Tarnow class I (10,23). Was established by Abdelraouf et al. that there was a greater reduction of black triangles because the baseline value was lower (5). Thus, we can conclude the larger the black triangle or the smaller the height of the interdental papilla, the more difficult it is to completely restore the papilla.

5.2) Gingival Phenotype

Histological features are one of the causes of the difficulty in reconstructing the interdental papilla. The thick gingival phenotype has been considered in several clinical procedures to be the most favourable compared to the thin gingival phenotype and so patients with thin gingival phenotype is not so beneficent. The reason seems to be, according to Ni et al., the thickness of the connective tissue layer differentiates the thin or thick gingival phenotype, and this layer contains more gingival fibroblasts and collagen fibers, so the thicker it is, the more fibroblasts proliferate and generate more collagen fibers when stimulated (24). In addition, the probe transparency method is indicated to define the type of gingiva phenotype. Basically, the probe is inserted into the sulcus, and if it is visible, the phenotype is thin (gingival thickness equal to or less than 1mm), if it is not visible, it is considered a thick phenotype (gingival thickness is greater than 1mm) (16). Therefore, is very important to identify what gingival phenotype our patient has so we can design the best treatment plan.

5.3) Injection with Hyaluronic Acid

Hyaluronic Acid must be chemically altered in order to avoid rapid degradation and therefore increase lifespan – prolonging its presence – through a cross-linking process, and thus instead of healing by reparation promotes regeneration (13,16). Several in our studies are usually modified. Although hyaluronic acid is fluid enough to penetrate the defect space, it is rigid enough to prevent the tissue from collapsing during the effect (25).

However, its use is contraindicated in patients with a tendency to develop hypertrophic scars, with autoimmune diseases or subject to immunotherapy treatments, with active herpes, allergic to heparin and chondroitin sulphate, in cancer patients and children and pregnant or lacting mothers (18). Report of a case by Sánchez et al. reported after 4 injections of HA that the papilla had returned to normal size compared to the height of the adjacent papilla. It was observed that the papilla moved towards the crown and covered the area of the interdental contact point, eliminating the black triangle (18).

Spano et al. conducted a clinical study in which they injected HA together with an overlay technique. By separating the papilla by tunnelling, a subperiosteal space could be created that allowed for greater mobilization of the papilla prior to injection. The results showed a papillary filling with only one application (10). A review by Çankaya et al. concluded over 2 years that the highest percentage fill was at 25 months compared to 3 months and 12 months. This demonstrates the very long-lasting effect of HA together with the patient's motivation to continue treatment and to maintain good oral hygiene. A clear synergistic effect is present (25). Although Abdelraouf et al. did a study comparing hyaluronic acid with saline solution and concluded that the HA group had better results than the saline group, although it did not complete the entire papilla. Therefore, there is a limitation in the injections of Hyaluronic Acid injections and is achieved in small defects of the papilla (5).

5.3.1) Technique

Of the studies collected, some administered anaesthesia and others did not, depending on the dentist and what they find more comfortable for the patient and if they want to be anesthetized. Regarding the anaesthesia used, Faour et al. used a topical anaesthetic spray (16), while Bertl et al. applied a 2% xylocaine gel with a 30-gauge needle. (17) On the other hand, the patients of Ni et al. received local infiltrative anaesthesia with 4% articaine (24), and the patients of Alhabashneh et al. received local anaesthesia at the mucogengival junction with a 30-gauge needle 5 minutes earlier to decrease pain caused by the various hyaluronic acid injections (6). It was not administered exactly at the site where the HA would be administered so that there is no interaction between the various constituents and to decrease the number of injections at the same site. In the clinical study by Çankaya et al., infiltrative anaesthesia was administered slightly away from the tip of the papilla where HA would be administered (25). Regarding the administration of HA, Sánchez et al. the needle was inserted perpendicular to the base with respect to the longitudinal axis of the tooth. It was injected until ischemia was observed (18). Alhabashneh et al. injected HA according to

the 3-step technique with a 30G x 16/1300 gauge needle, and it was inserted at a 45º angle with the bevel towards the bone, to decrease backtracking (6).

Consistently, in the studies by Spano et al. and Çankaya et al. administered HA with a 27-gauge needle (10,25). Likewise, in the study by Çankaya et al. the technique of HA administration is elaborated. An imaginary triangle is defined and 3 equidistant injections are administered, at each vertex of the triangle. When the needle was removed, the injection was continued. The amount was defined by pressure and tissue colour. The authors state that the gingiva should not turn white (25). In the comparative study by Mandel et al., the "three-step technique" is used, where a 30-gauge needle is used along the mucogengival junction at the base of the papilla at 4-5 sites, then in the attached gingiva at the base of the papilla in 2-3 places, and finally at the tip of the papilla at one place; 0,1ml per site (3). The study carried by Abdelraouf et al. chose to insert the needle 2-3mm apical to the tip of the papilla with a 45º along the axis of the tooth, and the bevel directed apically. The papilla was gently molded in an apical direction for 1 minute (5). Hyaluronic acid act within the collagen tissue and binds to molecules of the extracellular matrix and receptors on the cell surface, interacts, and results in the activation of signalling cascades. Consequently, it induces cell migration, proliferation and gene expression (6).

5.3.2) Postoperative Recommendations

With regard to postoperative recommendations, these also differ slightly. Patients in the study by Alhabashneh et al. were only instructed to maintain good oral hygiene, brush their teeth regularly with a soft-bristled brush and to use an antiseptic mouthwash 2x a day until the end of the study (6). In the study by Spano et al. a 0.12% chlorhexidine mouthwash was prescribed and iboprufen was taken when necessary (10). Accordingly, in the studies by Irribarra-Leigh et al. and Abdelraouf et al. abstinence from interproximal hygiene was instructed within 24 hours of treatment with HA (5,23).

5.4) Injection with Platelet-Rich Fibrin

PRF is organized as a dense fibrin skeleton that can vary is the number of platelets, leucocytes and growth factors. The advantages of using PRF are that it is not expensive, easy to acquire, is prepared in a few minutes, no donor is required, less invasive, less post-treatment discomfort, promotes faster healing and less oedema (8,22).

Ahila et al. to increase the interdental papilla with PRF, used the Han and Takei technique where a pedicle is formed using a semilunar incision in the entire papilla, maintaining a vascular supply without creating tension so that the gingiva does not rebound. The use of connective tissue grafts was avoided in this clinical study (26).

Purl et al. comment that despite the fact that it required several injections with PRF, with photographic clinical evaluation of the decrease in the area of the black triangle and reduction of the CP-PT distance, they obtained optimal aesthetic results and an admirable filling of the papilla tissue. The questionnaire given to the patients revealed that they were extremely pleased with the final result (27).

In this clinical study, Ozcan Bulut et al. reconstructed the platelet-rich fibrin papilla with connective tissue graft. The results showed that although PRF administration was successful, the connective tissue graft better reconstructed the papilla without recurrence of interdental papilla loss. Is due to the soft tissue stability and less dimensional change leading to better space maintenance due to the vascular network, cellular capacity and firm collagen matrix of the connective tissue. Connective tissue stability was more successful compared to PRF stability due to faster matrix resolution. Therefore, they do not recommend the use of PRF until there are improvements such as preparation and application techniques (8).

Singh et al. conducted a comparative study between PRF (group 1) and connective tissue (group 2). After evaluating the different variables, they commented that complete filling was 90% in group 1 and 95% in group 2; the distance of the interdental papilla was greater in group 2 (3.45mm) than group 1 (3.10mm); the height of the interdental papilla increased at month 1 and maintained until month 3 in group 1 and in group 2 there was a constant increase. Group 2 (CTG) showed better results overall, but regarding to discomfort, group 2 was more invasive. With both techniques, pleasant results are obtained that treat the absence of the papilla (22). This clinical trial served to prove the use of platelet-rich fibrin in combination with microneedling, conducted by Ozsagir et al. The MN+PRF group had a significant increase compared to the PRF group at 6 months, where the gingival thickness (main parameter) obtained was 44.19% (PRF) and 65.00% (MN+PRF). This increase at 6 months is due to neoangenesis and neocollogenesis. It is confirmed that it is possible to increase gingival thickness and the width of the keratinized tissue without surgical

procedures (21). Further studies are needed to study only the PRF effect, without complimentary materials, to better understand its potential.

5.4.1) Preparation of PRF

The preparation of PRF requires a 10mL blood sample without anticoagulants and activators obtained in glass tubes. It is then centrifuged at 700 rpm for 3 minutes according to Ozsagir et al., Puri et al. and Faour et al. (16,21,27). In disagreement, in the study by Singh et al. the sample was centrifuged at 3000 rpm for 12 minutes (22) and in the study by Ozcan Bulut et al. was centrifuged at 2700 rpm for 12 minutes (8). It is stated by Ozsagir et al. that low speed centrifugation allows the regeneration process as it is rich in platelets, leukocytes and growth factors (21). The top layer needs to be removed (8). The PRF, after 10-15 minutes, coagulates and forms a gel as the liquid fibrinogen converts to solid fibrin. It is important to inject at this time (21,27).

5.4.2) Technique

Regarding the anaesthesia administered before the injection with PRF, Ahila et al. reports that patients were anaesthetised with 0.2% xylocaine with 2% adrenaline (26). It is noted by Ozsagir et al. that anaesthesia should be administered before the obturation procedure, since it can affect the measurement of papillary thickness and the vasoconstrictor substances can affect the distribution of the PRF in the desired area (21). Regarding the technique used, Puri et al. inserted the needle 2-3mm apically to the tip of the papilla making a 45º angle along the axis of the tooth with the apically rotated bevel (27).

PRF promotes cell differentiation in the matrix, favouring tissue regenerating. Thus, after PRF injection, growth factors are released that induce the proliferation of new cells and fibroblasts are transformed into collagen and elastin fibers between day 5 and week 8. These new fibers develop from the process of neocollagenesis. Fibroblasts also promote angiogenesis by stimulating the proliferation of endothelial cells present in the vessels (21).

5.4.3) Postoperative Recommendations

Several postoperative recommendations were given, including oral hygiene with a soft brush and avoiding the interdental area (27), and taking medication: 0.12% chlorhexidine

antiseptic, 2x a day, for 14 days and anti-inflammatory, 2x a day, for 5 days (8). Singh et al. for their part, instructed to rinse with 0.2% chlorhexidine gluconate solution and avoid sanitizing the treated area. Medication such as amoxicillin 500mg, 3x a day for 5 days a combination of paracetamol (325mg) with diclofenac (50mg), 3x a day for 3 days, was also administered (22).

5.6) Adverse Reactions

We know that Hyaluronic Acid is used for aesthetic fillers due to its hydrodynamics, volume maintenance and tissue resistance. However, there are several reports of adverse reactions and necrosis after injection with Hyaluronic Acid. Two cases will be discussed in this dissertation (17). Reactions such as unilateral lip swelling, mucosal tenderness, erythema, pruritus, bruising, pain, paleness and small bumps have been reported and are considered mild. These reactions disappeared one week after the injection. One of the patients reported lip discolouration (livedo reticularis) a few hours after the injection and this decreased in intensity over time over the week.

However, it has been reported that injecting hyaluronidase after an adverse effect occurs is efficient in reducing complications, such as the effectiveness in preventing tissue necrosis after 24 hours. The injection of HA into the mucosa beyond the mucogengival junction makes it difficult to increase the papilla since the reservoir created would not allow it to migrate. This adverse effect can be explained by the hygroscopic attraction over time, which exerted an external vascular compression and partial obstruction of the adjacent blood vessels. So, it is advised not to inject above the mucogengival margin. This topic is important because even though the symptoms in these two reported cases disappeared within a week, it reminds and raises awareness that accidents and adverse reactions do occur and we should follow protocols to decrease their occurrence. Therefore, further studies are needed to establish protocols for treating adverse reactions that might appear.

5.7) Comparison between short-term and long-term results

As for hyaluronic acid, apart from its biological activity, it is also biodegradable. Consequently, it has a life span of 2 to 3 days and its metabolization occurs in the liver. The durability depends on the specific material, concentration, injection techniques and site.

Also, the type of papillary loss and size. Mandel et al. state that the long-term results are more dependent on the patient's interdental oral hygiene than on the type of hyaluronic acid. So much so that in patients where plaque accumulation was observed, there was no improvement compared to the initial loss (3). Sánchez et al. stated that at 28-30 days, collagen synthesis is accomplished (18). The clinical study by Çankaya et al. showed that the filling at 24 months was higher than at 3 and 12 months, which shows that the effect of HA is maintained and increased during the 24 months because HA absorbs water overtime (25). But since it tends to degrade naturally in the body, maintenance is critical. A general evaluation was made assessing the height of the papilla (CP-PT distance), the width of the keratinized tissue and gingival thickness, where it was concluded that it is not possible to define a mean value – maximum peak effect – since the variables are different in each article, both in HA and PRF. Therefore, the long-term stability of the papillary filling is unknown, success is varied and data is still scarce in the literature.

5.8) Overview

During this discussion, papilla classification, gingival phenotype, injection with both HA and PRF and their protocols, adverse reactions and comparison of results were analysed. Regarding how the material works in the connective tissue, there was not much information to collect. Other disadvantages are, since there are so many variables analysed in the different articles selected, it is impossible to determine the maximum peak effect on the papillae, and therefore it was not possible to establish a protocol for recall maintenance. Also, we only had access to 2 cases regarding adverse effects and it is possible that more such cases happen, but are not reported. So, diminishes their understanding and why they occur. Thus, it was not possible to establish a protocol to treat adverse reactions.

As regards the collection of data carried out in the articles, it shows low quality since some articles do not collect the measurement of the baseline or final papillae, do not have a follow-up that demonstrates their efficacy or the time analysed is very short, and do not mention the amount administered. There is, therefore, a discrepancy in the analyses.

Evaluating the articles referring to PRF, we conclude that more articles are needed to evaluate only its effect, without the presence of an adjuvant, as already exists with HA.

6 – CONCLUSION

The interdental papilla is essential, especially on anterior teeth, because acts like a biological barrier, and besides makes the smile more aesthetic. In addition, its absence can lead to phonetic problems, gingivitis and caries lesions. The causes are multifactorial, described throughout this dissertation.

We concluded the ideal conditions for restoring a papillary loss are that the black triangle should be as small as possible and the gingiva phenotype thick.

Confirming the Hypothesis, Hyaluronic Acid showed better results than Platelet-Rich Fibrin, although the latter is promising in the future. Both materials are biodegradable, i.e. they degrade naturally over time and there is a need to restore them. Long-term stability of papillary fill is unknow, so a more objective and in-depth evaluation is needed to establish a recall maintenance protocol.

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